



Cyclooxygenase-2 polymorphisms and susceptibility to gastric carcinoma: A meta-analysis

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RESULTS: Ten studies were retrieved reporting a total of 11 COX-2 polymorphisms. Carriers of -765C, -1195A, -1290G, *2430T alleles and *429TT genotype revealed increased risk for GC (OR = 1.71, 95% CI: 1.01-2.90, $P = 0.05$; OR = 1.58, 95% CI: 1.05-2.38, $P = 0.03$; OR = 1.55, 95% CI: 1.01-2.39, $P = 0.05$; OR = 2.62, 95% CI: 1.20-5.73, $P = 0.02$ and OR = 0.74, 95% CI: 0.59-0.95, $P = 0.02$, respectively).

CONCLUSION: The -765C, -1195A, -1290G, *2430T alleles and *429TT genotype of COX-2 polymorphisms were determined a significant association with susceptibility to GC.

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Key words: Cyclooxygenases-2; Gastric cancer; Polymorphisms; Susceptibility; Meta-analysis

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Abstract

AIM: To investigate the association of the cyclooxygenases-2 (COX-2) polymorphisms and susceptibility to gastric cancer (GC) by means of meta-analysis.

METHODS: Publications addressing the association between polymorphisms of COX-2 and susceptibility to GC were selected from the MEDLINE, EMBASE and CBMDisc databases. Data was extracted from the studies by 2 independent reviewers. The meta-analyses were performed by RevMan 5.0.23. From these data, odds ratio (OR) with 95% confidence interval (CI) was calculated.

INTRODUCTION

Gastric cancer (GC) is the fourth most common cancer and the second leading cause of cancer-related death worldwide^[1-3]. In 2008, around 21 500 people were diagnosed with gastric cancer and approximately 135 130 died of the disease in the United States^[4]. GC is a complex and multifactorial disease. The marked geographic variation, time trends, and the migratory effect on GC incidence suggest that environmental or lifestyle factors are major contribu-

tors to the etiology of this disease. Examples include: diet, lifestyle, *Helicobacter pylori* (*H. pylori*) infection and genetic material^[1].

Recent data has expanded upon the concept that inflammation is a critical component of tumor progression. Many cancers arise from sites of infection, chronic irritation and inflammation^[5]. Tumor microenvironment is largely orchestrated by inflammatory cells, which are an indispensable participant in the neoplastic process, fostering proliferation, survival and migration. Inflammation also plays an important role in the development and progression of GC^[6]. Epidemiological and animal data revealed that the use of non-steroidal anti-inflammatory drugs (NSAIDs) might reduce the risk of GC^[7]. NSAIDs primarily inhibit the activity of the cyclooxygenase enzymes (COXs) and thereby affect the synthesis of prostaglandin signalling molecules, which are involved in a wide range of physiological processes beyond inflammation^[8].

COXs catalyze the rate-limiting step in the production of prostaglandins (PG), bioactive compounds involved in processes such as fever and sensitivity to pain, and are the target of NSAIDs^[9]. In mammals, the two COXs genes encode a constitutive isoenzyme (COX-1) and an inducible isoenzyme (COX-2); both of which are of significant pharmacological importance^[9]. COX-1 is constitutively expressed in the majority of tissues and is associated with housekeeping functions such as vascular homeostasis and platelet aggregation^[10]. COX-2, which is highly inducible and almost undetectable under normal physiological conditions, is readily induced in response to mitogens, tumor promoters, cytokines, growth factors, stress-inducing agents promoting inflammatory reactions, and tumor development^[11]. COX-2 overexpression was found in a large proportion of GC tissues and was significantly associated with advanced tumor stage, *H. pylori* infection and lymph node metastasis^[12]. COX-2 may also play a role in gastric carcinogenesis, which was associated with inhibition of apoptosis, increased metastasis potential and neoangiogenesis^[13-16]. The expression of COX-2 is regulated by a complex signal transduction pathway in which many nuclear proteins interact with the COX-2 promoter region and play a decisive role in gene transcription^[17]. Therefore, single nucleotide polymorphisms (SNPs) in the COX-2 promoter may have a great impact on gene transcriptional activity by altering the binding capability with certain nuclear proteins, resulting in inter-individual variability in susceptibility to cancer^[18].

Systematic review can be a resourceful tool in detecting an association that could otherwise remain masked in the sample size studies, especially in those evaluating rare allele frequency polymorphisms^[19]. The aim of this meta-analysis was to investigate the association of the COX-2 polymorphisms with susceptibility to GC by conducting a meta-analysis from all eligible case-control studies published to date.

MATERIALS AND METHODS

Search strategy and identification of studies

Medline, EMBASE and CBMDisc databases search were

performed to retrieve papers linking COX-2 polymorphisms and susceptibility to GC available online by April 2010 without language restrictions, using the following query: [COX 2 OR COX-2 OR COX2 OR PEGS2 OR PEGS-2 OR "Cyclooxygenase 2" (MeSH)] AND [polymorphism OR polymorphisms OR "Polymorphism, Genetic" (MeSH) OR "Polymorphism, Single Nucleotide" (MeSH)] AND [gastric cancer OR "Stomach Neoplasms" (MeSH)]. The reference lists of major textbooks, review articles, and of all the included articles identified by the search were then individually searched to find other potentially eligible studies.

Inclusion criteria

To be eligible for inclusion in this meta-analysis, the following criteria were established: (1) the study must include a case-control study that addressed GC patients and normal or benign gastric diseases controls; (2) the study must have evaluated the COX-2 polymorphisms and susceptibility to GC; and (3) the study must have included sufficient data for extraction.

Exclusion criteria

Studies were excluded from consideration if: (1) the study was based on family data or incomplete raw data; (2) the study did not have the outcomes of comparison reported or it was not possible to determine them; or (3) the study contained a smaller sample size (number of cases < 30) and overlapped others.

Data extraction and quality assessment

Using a standardized form, data from published studies were extracted independently by two investigators (Liu JL and Liang Y) to populate the necessary information. From each of the included articles the following information was extracted: first author, year of publication, country, ethnicity, study design, source of cases, sample size, histological type, polymorphisms of genes, histopathological confirmations and evidence of Hardy-Weinberg equilibrium (HWE).

The quality of papers was also independently assessed by two researchers (Liu JL and Xing LL) based on the STROBE quality score systems^[20]. 39 items relevant to the quality appraisal were used for assessment, scores ranged from 0 (lowest) to 50 (highest)^[21]. Main items for quality assessment included: title and abstract, introduction, methods, study design, setting, participants, variables of interest, bias, HWE, sample size, statistical methods, funding and disclosure statement, internal validity, descriptive data, outcome data, main results, discussion, limitations, generality and interpretation^[20,21].

Statistical analysis

Individual or pooled odds ratio (OR) and 95% confidence interval (CI) were calculated for each study using Review Manager version 5.0.23 software (provided by The Cochrane Collaboration, Oxford, England)^[22]. Between-study heterogeneity was estimated using the χ^2 -based Q statistic^[23]. Heterogeneity was considered statistically

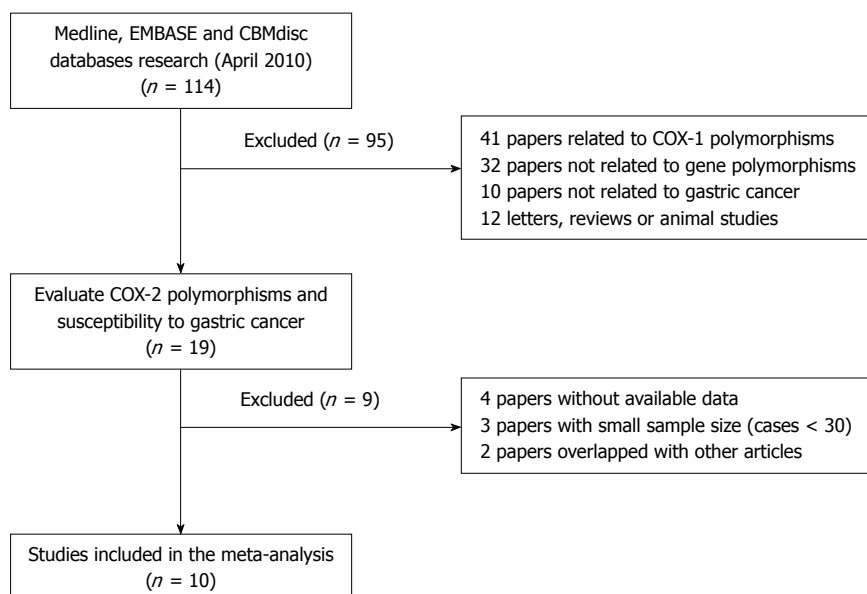


Figure 1 Flow chart showing study selection procedure. COX: Cyclooxygenases.

significant when $P_{\text{heterogeneity}} < 0.01$ or $I^2 > 50\%$. If heterogeneity existed, data was analyzed using a random effects model. In the absence of heterogeneity, a fixed effects model was used. Sources of heterogeneity were appraised by subgroup stratification analysis, based on several study characteristics, such as ethnicity and source of control individuals (population or hospital based). The funnel plot method was used to assess the possible presence of publication bias^[24].

Before the effect estimation of the several COX-2 polymorphisms in gastric carcinogenesis, the HWE was assessed for all the polymorphisms in each study. A χ^2 test was performed to examine HWE when genotype data was available. If HWE disequilibrium existed ($P < 0.05$), or it was impossible to evaluate this equilibrium, sensitivity analysis was performed.

RESULTS

Search results

The search strategy retrieved 114 potentially relevant papers (52 in Medline, 35 in Embase, 27 in CBMdisc). There were 10 studies included in this meta-analysis. One-hundred and four studies were subjected to a full text review and excluded according to the selection criteria stated above. The flow chart of study selection is summarized in Figure 1.

Study characteristics and quality

In total, 3074 GC cases from 10 case-control studies were included in the meta-analysis. All studies were considered as case-control studies. Five ethnicities were addressed: two studies focused on Caucasian populations^[25,26], five on Asian populations^[27-31], one on a Hispanic population^[32], one on a Dutch population^[18] and one on an Indian population^[33]. Eight studies^[18,25,26,28-31,33] used hospital-

based cases and controls and two studies^[27,32] described a population-based design. Cases and controls of four studies^[25,27,30,32] were mainly defined through endoscopic multiple biopsies procedures and three studies^[18,31,33] through endoscopy, with histological assessment. However, there were three studies^[26,28,29] that did not mention the method of confirmation. The characteristics and methodological quality of all studies are summarized in Table 1.

The characteristics of COX-2 polymorphisms in gastric cancer

Eleven COX-2 polymorphisms were addressed in gastric carcinogenesis: -765G>C, -1195G>A, Gly587Arg(G>A), 1290A>G, 8473T>C, IVS5-275T>G, IVS7+111T>C, V102V, *429T>C, *2430C>T, 587codonG>A. The genotype distribution of COX-2 polymorphisms and the variant allele frequency are described in Table 2. A HWE test was performed on all included studies, all of them showed in HWE ($P > 0.05$).

Association between COX-2 polymorphism and gastric cancer

Meta-analysis of eight studies identified a significant association between the -765C allele and susceptibility to GC (OR = 1.71, 95% CI: 1.01-2.90, $P = 0.05$) using the random effects model ($P_{\text{heterogeneity}} < 0.00001$, $I^2 = 89\%$). The -1195G>A COX2 polymorphism analysis revealed that the -1195A allele was also a risk factor for susceptibility to GC (OR = 1.58, 95% CI: 1.05-2.38, $P = 0.03$) using the random effects model ($P_{\text{heterogeneity}} = 0.04$, $I^2 = 70\%$). The -1290A>G analysis showed that the -1290G allele was a risk factor for GC (OR = 1.55, 95% CI: 1.01-2.39, $P = 0.05$). The *429T>C analysis also revealed that a significant association between the *429T allele and susceptibility to GC (OR = 0.74, 95% CI: 0.59-0.95, $P = 0.02$) using the fixed effects model ($P_{\text{heterogeneity}} = 0.42$, I^2

Table 1 Characteristics and quality assessment of 10 included case-control studies

Study	Yr	Country	Ethnicity	Polymorphisms of COX-2	No. of participants	Quality scores
Pereira <i>et al</i> ^[25]	2006	Portugal	Caucasians	-765G>C	73 ^a /210 ^c	33
Liu <i>et al</i> ^[27]	2006	China	Asians	-765G>C, -1195G>A, Gly587Arg(G>A)	248 ^a /427 ^c	33
Zhang <i>et al</i> ^[28]	2006	China	Asians	-765G>C, -1195G>A, -1290A>G	323 ^a /646 ^c	28
Jiang <i>et al</i> ^[29]	2007	China	Asians	-1195G>A, 8473T>C	254 ^a /304 ^c	36
Hou <i>et al</i> ^[26]	2007	Poland	Caucasians	-765G>C, IVS5-275T>G, IVS7+111T>C, V102V(G>C), *429T>C, *2430C>T	464 ^a /480 ^c	33
Canzian <i>et al</i> ^[32]	2008	Venezuela	Hispanics	IVS5-275T>G, V102V, *429T>C	1169 ^a /1863 ^b	39
Zhu <i>et al</i> ^[30]	2008	China	Asians	-765G>C, 587codonG>A	140 ^a /125 ^c	37
Saxena <i>et al</i> ^[33]	2008	India	Indians	-765G>C	62 ^a /241 ^d	34
Sitarz <i>et al</i> ^[18]	2008	Netherlands	Dutch	-765G>C	241 ^a /100 ^c	31
Tang <i>et al</i> ^[31]	2009	China	Asians	-765G>C	100 ^a /105 ^c	29

^aGastric cancer; ^bPrecancerous gastric lesions; ^cHealthy controls; ^dBenign gastric diseases. COX-2: Cyclooxygenases-2.

Table 2 The genotype distribution of COX-2 polymorphisms and the variant allele frequency *n* (%)

Polymorphism	Study	Cases		Controls		Variant allele frequency	OR (95% CI)
		<i>n</i>	Variant allele carriers	<i>n</i>	Variant allele carriers		
-765G>C	Pereira <i>et al</i> ^[25]	73	37 (51)	210	80 (38)	0.22	1.67 (0.98-2.86)
	Liu <i>et al</i> ^[27]	388	42 (11)	427	43 (10)	0.05	1.08 (0.69-1.70)
	Zhang <i>et al</i> ^[28]	323	35 (11)	646	26 (4)	0.02	2.90 (1.71-4.91)
	Hou <i>et al</i> ^[26]	290	80 (28)	409	121 (30)	0.16	0.91 (0.65-1.27)
	Zhu <i>et al</i> ^[30]	140	38 (27)	125	20 (26)	0.06	1.96 (1.07-3.59)
	Saxena <i>et al</i> ^[33]	62	48 (77)	241	70 (29)	0.16	8.38 (4.34-16.16)
	Sitarz <i>et al</i> ^[18]	241	65 (27)	100	41 (41)	0.25	0.53 (0.33-0.87)
	Tang <i>et al</i> ^[31]	100	45 (45)	105	29 (28)	0.06	2.14 (1.20-3.84)
Pooled OR = 1.71 (1.01-2.90)							
-1195G/A	Liu <i>et al</i> ^[27]	389	316 (81)	427	322 (75)	0.50	1.41 (1.01-1.98)
	Zhang <i>et al</i> ^[28]	323	291 (90)	646	510 (79)	0.52	2.43 (1.61-3.66)
	Jiang <i>et al</i> ^[29]	254	206 (81)	304	242 (80)	0.26	1.17 (0.77-1.77)
Pooled OR = 1.58 (1.05-2.38)							
Gly587Arg (G>A)	Liu <i>et al</i> ^[27]	386	18 (15)	407	23 (6)	0.03	0.82 (0.43-1.54)
	Zhang <i>et al</i> ^[28]	323	40 (12)	646	54 (8)	0.04	1.55 (1.01-2.39)
-1290A>G	Jiang <i>et al</i> ^[29]	254	95 (37)	304	105 (34)	0.11	1.13 (0.80-1.60)
	Hou <i>et al</i> ^[26]	311	93 (30)	421	123 (29)	0.16	1.03 (0.75-1.42)
IVS5-275T>G	Canzian <i>et al</i> ^[32]	108	36 (33)	1003	392 (39)	0.22	0.78 (0.51-1.19)
Pooled OR = 0.93 (0.71-1.21)							
IVS7+111T>C	Hou <i>et al</i> ^[26]	299	78 (26)	421	114 (27)	0.15	0.95 (0.68-1.33)
	Hou <i>et al</i> ^[26]	302	72 (24)	410	125 (30)	0.16	0.71 (0.51-1.00)
	Canzian <i>et al</i> ^[32]	115	32 (28)	1053	214 (20)	0.11	1.51 (0.98-2.3)
Pooled OR = 1.03 (0.49-2.14)							
*429T>C	Hou <i>et al</i> ^[26]	304	167 (55)	165 (40)	251 (60)	0.36	0.80 (0.59-1.08)
	Canzian <i>et al</i> ^[32]	53 (49)	56 (51)	398 (38)	644 (62)	0.38	0.65 (0.44-0.97)
Pooled OR = 0.74 (0.59-0.95)							
*2430C>T	Hou <i>et al</i> ^[26]	289 (94)	19 (6)	399 (98)	10 (2)	0.01	2.62 (1.20-5.73)
587codonG>A	Zhu <i>et al</i> ^[30]	121 (86)	19 (14)	112 (90)	13 (10)	0.06	1.35 (0.64-2.87)

n: No. of patients; OR: odds ratio; 95% CI: 95% confidence interval; COX-2: Cyclooxygenases-2.

= 0%). A significant association with the susceptibility to GC was also determined in the *2430T allele analysis (OR = 2.62, 95% CI: 1.20-5.73, *P* = 0.02) (Figure 2). However, the Gly587Arg(G>A), 8473T>C, IVS5-275T>G, IVS7+111T>C, V102V and 587codonG>A polymorphisms showed no association with the susceptibility to GC (OR = 0.82, 95% CI: 0.43-1.54, *P* = 0.53; OR = 1.13, 95% CI: 0.80-1.60, *P* = 0.48; OR = 0.93, 95% CI: 0.71-1.21, *P* = 0.58; OR = 0.95, 95% CI: 0.68-1.33, *P* = 0.77; OR = 1.03, 95% CI: 0.49-2.14, *P* = 0.95 and OR = 1.35, 95% CI: 0.64-2.87, *P* = 0.43, respectively).

Subgroup analysis was performed on -765G>C poly-

morphism by ethnicity, such as Caucasian, Asian, Indian and Dutch. Results showed no significant association between the -765C allele and susceptibility to GC in Caucasians (OR = 1.19, 95% CI: 0.65-2.15, *P* = 0.58), while an obviously significant association was determined in Asians (OR = 1.87, 95% CI: 1.19-2.94, *P* = 0.006) and Indians (OR = 8.38, 95% CI: 4.34-16.16, *P* < 0.00001). However, the results showed that the -765C allele was a protective factor for GC in Dutch (OR = 0.53, 95% CI: 0.33-0.87, *P* = 0.01) (Figure 3). Sensitivity analysis was performed after excluding studies conducted by Saxena *et al*^[33] and Sitarz *et al*^[18], because of the anomalous OR and rare ethnicity.

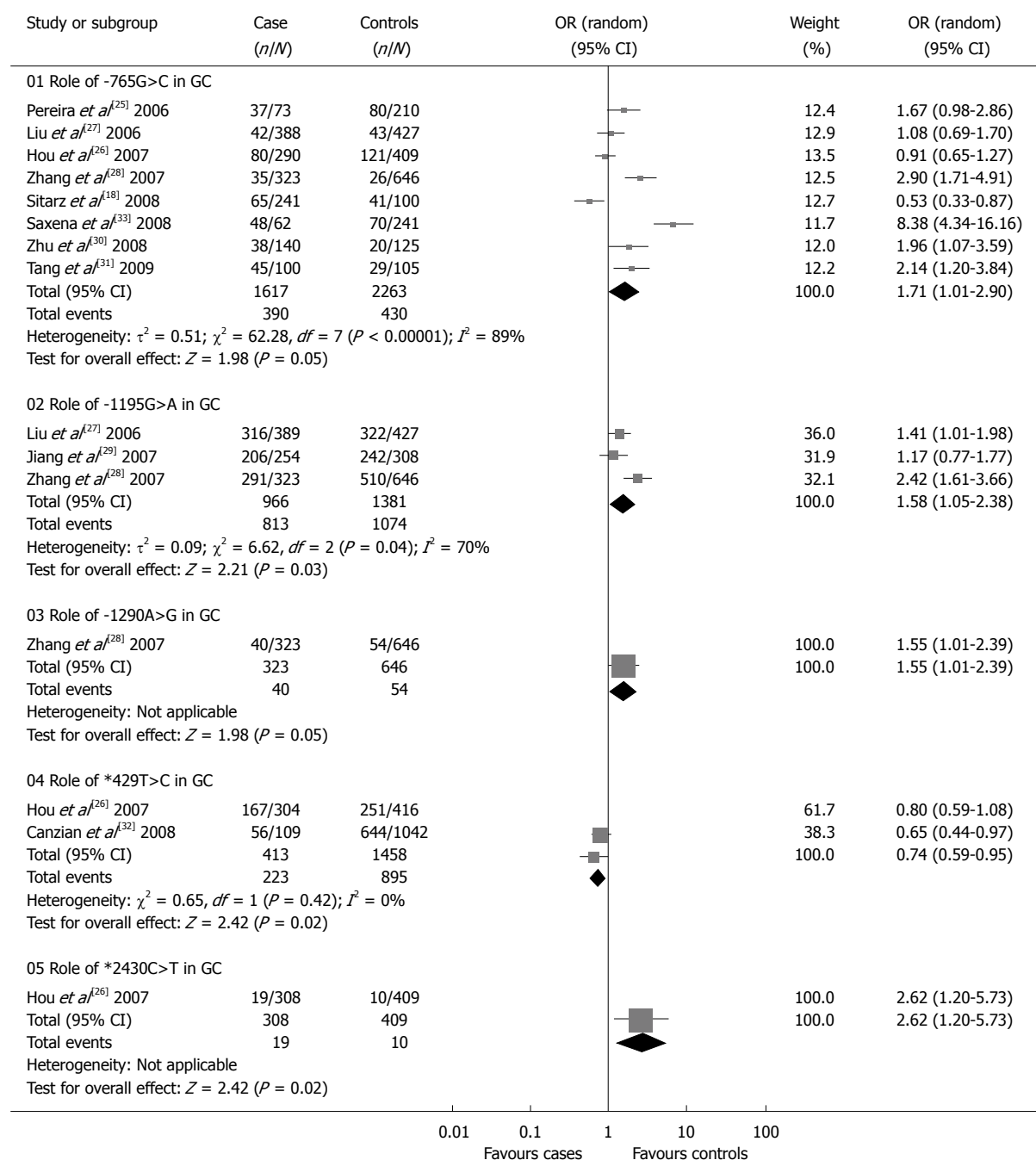


Figure 2 Meta-analysis of the association between cyclooxygenases-2 polymorphisms and susceptibility to gastric cancer.

No significant differences were observed between before and after results (OR = 1.59, 95% CI: 1.08-2.35, $P = 0.02$) (Figure 4).

Publication bias

The publication bias of the meta-analysis on the association between COX-2 and GC was detected by the funnel plot on -765G>C. The graphical funnel plot of 8 studies of -765G>C polymorphism appeared to be asymmetrical (Figure 5). Publication bias might occur if smaller studies showed no significant results remain unpublished, leading to an asymmetrical appearance of the funnel plot with a gap at the bottom of the graph.

DISCUSSION

Evidence suggests that COX-2 plays an important role in the carcinogenesis pathway, such as in the inhibition of apoptosis, tumor growth, angiogenesis, invasion and metastasis^[34-36]. The specific function of COX-2 in the formation of prostaglandins makes it a strong candidate for increasing susceptibility to common cancers such as GC, colorectal cancer, lung cancer and other cancers^[37]. As is known, genetic polymorphisms altering the level of protein expressed would be anticipated to have a substantial influence on disease activity. Several polymorphisms in COX-2 have been reported previously, although some

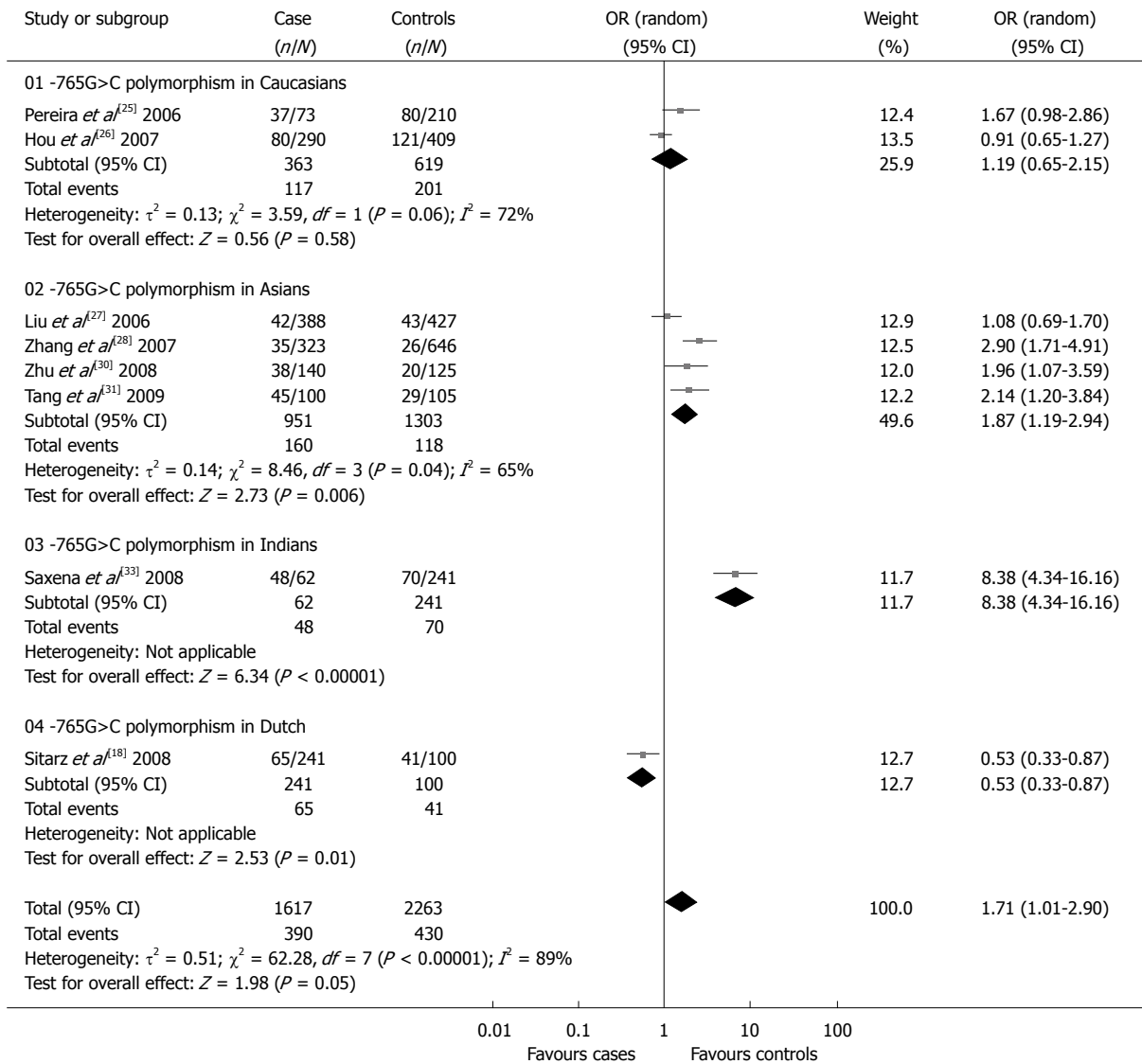


Figure 3 Subgroup analysis of -765G>C polymorphism by ethnicity.

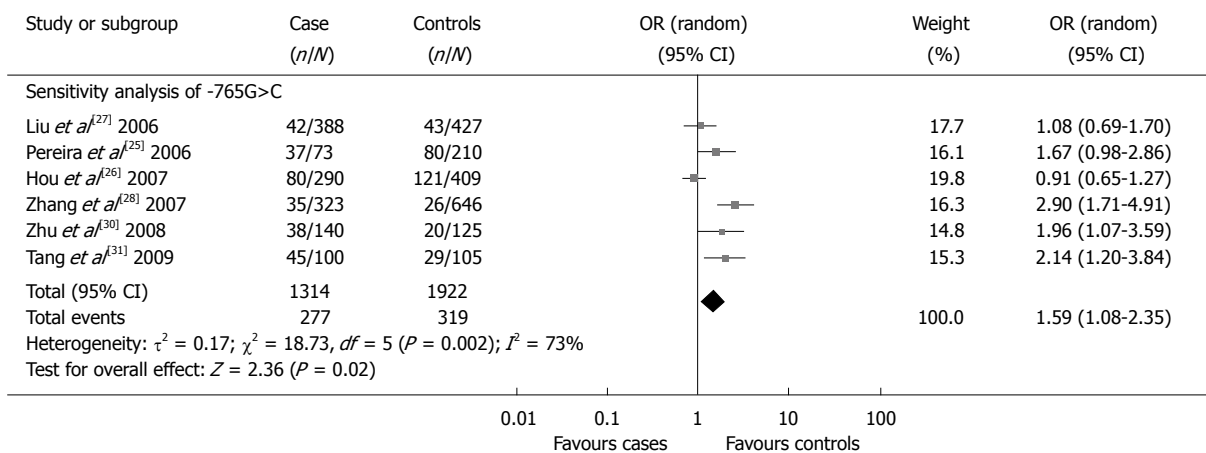


Figure 4 Sensitivity analysis of -765G>C polymorphism.

of these polymorphisms are not functionally significant or associated with susceptibility to cancer^[21]. There were also many polymorphisms of COX-2 gene which were

determined to have a significant association with the susceptibility to GC^[21,38].

Our meta-analysis quantitatively assessed the asso-

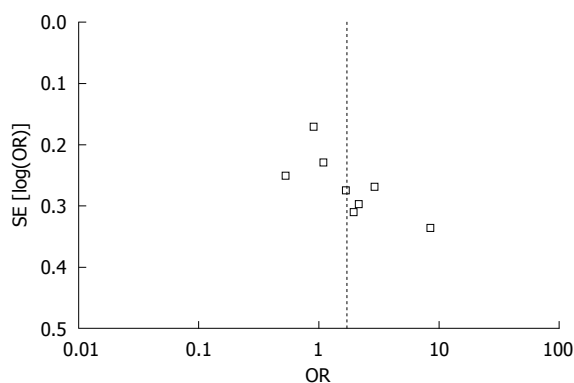


Figure 5 Funnel plots to explore publication bias.

ciation between COX-2 polymorphisms with the susceptibility to GC. Finally, 10 case-control studies were included and assessed. In this meta-analysis, 11 COX-2 polymorphisms were addressed and evaluated in gastric carcinogenesis: -765G>C, -1195G/A, Gly587Arg(G>A), 1290A>G, 8473T>C, IVS5-275T>G, IVS7+111T>C, V102V, *429T>C, *2430C>T, 587codonG>A. -765G>C, the most common polymorphism of the COX-2 gene and investigated in eight studies, revealed an increased risk behavior associated with gastric carcinogenesis in the normal population (OR = 1.71, 95% CI: 1.01-2.90, $P = 0.05$). As strong heterogeneity was reported, an ethnicity-based subgroup analysis was performed. The results showed that no association between the -765C allele and the susceptibility to GC in Caucasians, but an obviously significant association was determined in Asians (OR = 1.87, 95% CI: 1.19-2.94, $P = 0.006$) and Indians (OR = 8.38, 95% CI: 4.34-16.16, $P < 0.00001$). Interestingly, the -765C allele was a protective factor for GC in Dutch (OR = 0.53, 95% CI: 0.33-0.87, $P = 0.01$). Three studies discussed the association of the -1195G>A polymorphism and the susceptibility to GC. The results of the pooled analysis indicated that the -1195A allele was a risk factor for susceptibility to GC (OR = 1.58, 95% CI: 1.05-2.38, $P = 0.03$). In the study carried out by Zhang *et al.*^[28], the increased susceptibility was higher in individuals that were -1290G allele carriers (OR = 1.55, 95% CI: 1.01-2.39, $P = 0.05$). Unlike most of the COX-2 polymorphisms addressed, the *429C allele seems to play a protective role in GC development. However, the *429T allele was a risk factor for susceptibility to GC (OR = 0.74, 95% CI: 0.59-0.95, $P = 0.02$). Another study worth mentioning is the one by Hou *et al.*^[20], where we observed an increased risk of GC in Caucasians population with the *2430T allele (OR = 2.62, 95% CI: 1.20-5.73, $P = 0.02$). Unfortunately, no statistically significant results were observed in the Gly587Arg(G>A), 8473T>C, IVS5-275T>G, IVS7+111T>C, V102V and 587codonG>A COX-2 polymorphisms in gastric carcinogenesis. Therefore, in further functional studies, future investigations should focus on the -765G>C, -1195G>A, -1290A>G, *429T>C, and *2430C>T COX-2 polymorphisms and their molecular mechanism involving gastric carcinogenesis.

There were some limitations in our meta-analysis.

Firstly, because of incomplete raw data or publication limitations, some relevant studies could not be included in our analysis. Secondly, we were not able to address the sources of heterogeneity that existed among studies for most polymorphisms. However, we could not perform subgroup stratification analysis for the limited number of published studies. Thirdly, the lack of genotype frequency information provided by some published studies did not allow the estimation of the best genetic model of inheritance to follow. Although we actively contacted the authors, they did not provide a comprehensive set of data. In addition, the small sample size available was not ideal for detecting small genetic effects. Finally, our systematic review was based on unadjusted data, as the genotype information stratified for the main confounding variables was not available in the original papers and also the confounding factors addressed across the different studies were variable.

In conclusion, our meta-analysis of 10 case-control studies demonstrated an association between the -765C, -1195A, -1290G, *2430T alleles and *429TT genotype of COX-2 polymorphisms and GC. In addition, all of these findings suggested that ethnicity was the main sources of heterogeneity, and different ethnicities with COX-2 polymorphisms had varying susceptibility to GC. From the analysis, we also concluded that the Gly587Arg(G>A), 8473T>C, IVS5-275T>G, IVS7+111T>C, V102V and 587codonG>A polymorphisms showed no association with susceptibility to GC. As few studies are available in this field and current evidence remains limited, the necessity should be emphasized to conduct large studies with an adequate methodological quality, properly controlling for possible confounds in order to obtain valid results.

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COMMENTS

Background

Accumulated evidence indicates that the cyclooxygenases-2 (COX-2) play an important role in gastric carcinogenesis, which was associated with inhibition of apoptosis, increased metastasis potential and neoangiogenesis. To investigate the association of COX-2 polymorphisms with susceptibility to gastric cancer (GC), the authors carried out a meta-analysis of all related case-control studies.

Research frontiers

Much attention has been paid to the potential role of COX-2 in gastric carcinogenesis. Some of them have been trying to confirm the definite relationship between COX-2 polymorphisms and susceptibility to GC, and meanwhile, others attempt to uncover underlying mechanisms.

Innovations and breakthroughs

The current study demonstrated that the -765C, -1195A, -1290G, *2430T alleles and *429TT genotype of COX-2 polymorphisms have significant association regarding the susceptibility to GC.

Applications

Meta-analysis suggests that the -765C, -1195A, -1290G, *2430T alleles and *429TT genotype of COX-2 polymorphisms were statistically significant risk

factors for GC. These genetic profiles may enable clinicians to select individuals for early diagnosis strategies, diverse management schedules such as the follow-up of patients with GC, or even to propose selective COX-2 inhibitors or nonspecific COX inhibitors in patients with precancerous lesions.

Terminology

Meta-analysis is a statistical tool in detecting an association that could otherwise remain masked in the sample size studies, especially in those evaluating rare allele frequency polymorphisms.

Peer review

This is an interesting and good paper, the described analysis has been performed with precision and accuracy.

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